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Gravitational Force and the Cardiovascular System[1]

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Over millions of years man has evolved from a water breather in a weightless environment to an air breather in a 1-G environment. This gradual evolution allowed the development of structural and functional changes in both the respiratory and cardiovascular control mechanisms that allow man to cope with specific stresses in his normal habitat. In the area of cardiovascular performance, we have come to rely heavily on complex feedback responses to cope with postural changes, which alter the body axis along which gravitational forces act. The activities of daily living evoke these reflexes as we stand, sit, lie down, or become immersed. Over the past several years, many individuals have 'returned' to a weightless state during space missions whose duration has ranged from a few hours to several months. Missions related to space are likely to increase the time of exposure to the weightless condition. However, some of the mechanisms that are operative at 1-G appear to 'fail' when the 1-G load is reapplied following exposure to a period of weightlessness. There is indisputable evidence that, in some cases, the space environment, by relieving gravitational stresses, has permitted adaptive mechanisms to lapse, causing serious problems upon return to the 1-G condition. If man is to function in a space environment on a periodic basis, he must be able to adjust not only to weightlessness but also to the effects of the earth's gravity upon re-entry and, with a view to the future, to the gravitational fields of other planets that may eventually be reached.

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Successful adaptation to the space environment as we know it requires man to perform work. Cardiovascular feedback mechanisms must cope with two stresses, often combined: postural changes combined with changes in gravitational forces, and physical exercise. Appropriate responses to these stresses may be more difficult to achieve after adaptation to the weightlessness of space; in fact, man may not be able to fully adjust to the stress of gravity unless appropriate feedback responses are reinforced continuously during flight. Although many studies have been conducted prior to, during, and after space flight, due to logistic constraints, information to address the problems stated above is insufficient. To compensate for this lack of information, ground-based simulation studies have been conducted by us and others in an attempt to add insight into the problems of the cardiovascular adaptation to alterations in gravitational force.

The purpose of the present paper is to consider cardiovascular responses to changes in gravitational force. Man is ideally suited to his 1-G environment. Although cardiovascular adjustments are required to accommodate to postural changes and exercise, these are fully acomplished for short periods (min). More challenging stresses are those of short-term microgravity (h) and long-term microgravity (days) and of gravitational forces greater than that of earth. The latter can be simulated in the laboratory and quantitative studies can be conducted.

Weightlessness

Acute Exposure

When a person is standing in air, a large volume of blood is pooled in the periphery. This does not present a problem insofar as venous return (VR) is generally sufficient to maintain a stroke volume (SV) which, when combined with increased heart rate (HR), positive inotropic tone and venomotor tone, result in a cardiac output ($\dot{Q}$) that is sufficient to perfuse tissue to supply needed nutrients as well as to maintain mean arterial blood pressure. These cardiovascular responses are regulated by complex feedback mechanisms that meet the existing demands as well as the imposed stress of physical exercise. A decrease in the gravitational force results in less peripheral pooling, causing a cephalad shift of blood. This occurs when we assume the supine position or in the head down tilt position (HDT) and results in translocation of 200–500 ml of blood to the thorax. A further shift of blood can be accomplished by applying a graded differential pressure

either from below the diaphragm (lower body positive pressure, LBPP) or a graded differential pressure from distal to proximal (water immersion in water of thermoneutral temperature, WI).

During WI to the neck, ~800 ml of blood are translocated to the thorax [1]. The result of these graded increases in thoracic volume are increases in central venous pressure (CVP), right atrial pressure (P_{RA}) and end diastolic volume (EDV); typically heart rate and cardiac contractility remain unchanged. The outcome of these primary changes is an increase in stroke volume and cardiac output. An increase in $\dot{Q}$ could result in an increase in mean arterial pressure ($\bar{P}a$); however, this is not usually observed during weightlessness. $\bar{P}a$ does not increase because of a drop in total peripheral resistance (TPR) that is proportional to the increased $\dot{Q}$. The decrease in TPR is the result of increased blood flow to many vascular beds including skeletal muscle [3, 19].

One of the most striking responses to WI is the development of a diuresis and natriuresis [12]. The diuresis develops rapidly (with 2 h of WI) while the natriuresis develops more slowly, reaching a peak in 3–4 h. An increase in free water clearance is more marked in normally hydrated subjects as compared to hydropenic subjects [4] with little change in glomerular filtration rate or renal blood flow [12].

Gauer and co-workers [14–16] postulated that the diuresis is due to the inhibition of antidiuretic hormone (ADH), induced by stimulation of the left atrial volume receptors resulting from cardiac stretch (increased pressure and volume). The consequences of the diuresis were postulated to be a reduction in plasma volume (PV) and consequently decreased thoracic blood volume and SV. Initial studies supported this postulate [12]; however, recent studies clearly demonstrate that the cardio-renal coupling is not necessarily as tight as once thought [7, 17].

Data for HDT experiments from several investigators are presented in table I along with our data collected in the supine position and during WI. As indicated in table I, CVP, $\dot{Q}$ and SV increased initially during HDT while HR and $\bar{P}a$ were not changed significantly. After these initial changes, CVP, $\dot{Q}$ and SV decreased along with HR while $\bar{P}a$ did not change significantly. Although the magnitude of these changes in the supine position was less (~5%) and during WI greater (~15%), the overall pattern of the responses was similar in the three conditions. Most importantly, the initial increase in $\dot{Q}$ is offset by a decrease in TPR as $\bar{P}a$ did not change. Over the first 2–3 h of either HDT (6 °) or WI, HR and SV decreased, the result being a decrease in $\dot{Q}$. During HDT the CVP decreased to control levels after 5 h, which could

response, the renal responses to WI (both diuretic and natriuretic) were markedly attenuated in trained subjects [7]. The latter finding was accompanied by the lack of an ADH response; plasma-renin-angiotensin (PRA) and aldosterone responses remained normal. The dissociation of cardio-renal responses can be further demonstrated by the nocturnal attenuation of renal responses to WI; cardiac responses are unaltered [27]. The lack of a tight coupling of the cardiac-renal-endocrine responses to WI strongly suggests that while the Gauer-Henry mechanisms may play an important role in eliciting renal-endocrine responses to WI, other mechanisms must contribute to the overall outcome. Furthermore, the renal-endocrine responses do not alter PV over 8 h of WI while SV is decreasing to control levels.

Chronic Exposure

In spite of the absence of changes in PV over an 8-hour period, CVP continued to decrease to only 20% of the pre-HDT values during a 6-day HDT study; $\dot{Q}$ and SV did not decrease further [18, 22]. This finding during HDT agrees with data collected over 2–3 days of space flight where CVP and $\dot{Q}$ were not elevated over control levels; there was, however, a significant diuresis and PV decrease [21, 26, 29]. These 'second phase responses' to microgravity apparently contribute to the cardiovascular deconditioning observed after space flights. The exact mechanism of these responses needs further investigation. Apparently after 7 h of microgravity, CVP and $\dot{Q}$ as well as $\bar{P}a$ and PV are not elevated above 1-G levels. The question remains as to cause of the second phase of responses to microgravity. A partial explanation may be advanced that is related to the hydration state of the subjects during the 2 to 7-day experiments. The hydration state of these subjects is not well-explained; however, in our supine and WI experiments water loss was not repleted. In previous experiments in which water loss was repleted [4, 12], $\dot{Q}$ remained elevated, and the diuresis persisted over a 4-hour period. In these experiments $\dot{Q}$ was sustained at a high level during WI in spite of a decrease in SV. The effect of partial rehydration during microgravity might be to support the cardiac stretch which could lead to the continuation of the diuresis. Assuming that this tissue fluid loss is maximal, the second phase diuresis could result in a net loss of PV. This postulate needs further investigation; however, there is indisputable evidence that in some cases a microgravity environment, by relieving the stresses of gravity, allows adaptive mechanisms to lapse, resulting in what has been termed cardiovascular deconditioning.

Table I. Cardiovascular responses to head down tilt (HDT), supine (S), and water immersion (WI)

		Time							
		0 h (seated)	1 h	2 h	3 h	4 h	5 h	6 h	7 h
CVP, mm Hg	HDT	3.9	3.6	4.6	4.4	–	3.8	–	3.8
$\dot{Q}$, liters · min^{-1}	HDT	6.5	7.9	7.8	7.2	–	6.9	–	6.9
	S	6.7	7.6	7.1	6.9	7.0	6.7	6.6	6.9
	WI	6.8	8.8	7.4	7.2	7.0	7.0	7.2	7.1
SV, ml	HDT	94	114	116	110	–	106	–	106
	S	93	106	101	101	107	105	101	104
	WI	92	122	107	109	105	107	109	107
HR, beats · min^{-1}	HDT	69	69	67	65	–	65	–	65
	S	72	72	70	68	66	64	65	66
	WI	74	72	69	66	67	65	66	66
$\bar{P}a$, mm Hg	HDT	97	95	101	98	–	94	–	96
	S	89	86	89	87	88	86	87	88
	WI	88	89	90	88	87	86	87	86
PV, %	HDT	100	101	104	106	105	103	104	101
	S	100	101	102	101	100	99	99	99
	WI	100	104	103	100	100	99	99	98

account for the decreases in SV. During HDT, however, Echt has shown that CVP remains elevated for at least 4 h while SV decreases [11]. During WI, the decreased SV must be due to decreased cardiac contractility, presumably due to a decrease in sympathetic tone. Furthermore, PV, after an initial hemodilution, was not significantly less after 7 h of HDT, S or WI.

All three simulated microgravity experiments resulted in increases in cardiac stretch, urine flow and sodium excretion which were accompanied by a lower plasma renin, aldosterone, and ADH; a careful examination of the results indicate that these changes do not necessarily take place in a parallel manner. For instance, in sedentary subjects, the $\dot{Q}$ increases 35–40% during WI with an increased SV; however, within 2 h of WI it returns to control levels. On the other hand, both the diuresis and natriuresis are sustained for 2–4 h during WI. This dissociation between cardio-renal responses to WI was most dramatically demonstrated in endurance-trained athletes. In these subjects, WI initiates a greater increase in $\dot{Q}$ than in sedentary subjects; furthermore, it is sustained longer. Despite the cardiac

Table III. Resting cardiovascular responses to prolonged exposure to + G_z

Variable	+ G_z	Exposure time				
		4 min	12 min	20 min	28 min	32 min
$\dot{V}_{O_2}$, liters · min^{-1}	2	0.24	0.26	0.28	0.29	–
	3	0.41	0.49	0.61	–	–
$\dot{Q}$, liters · min^{-1}	2	4.4	4.5	4.4	4.4	–
	3	5.6	5.0	4.6	–	–
SV, ml	2	51	48	44	51	–
	3	47	35	32	–	–
HR, beats · min^{-1}	2	87	94	99	86	–
	3	120	142	140	–	–
$(Ca–C\bar{v})_{O_2}$, liters $O_2 \cdot l_b^{-1}$	2	5.4	5.8	5.2	6.6	–
	3	7.3	9.8	13.3	–	–

arterio-venous oxygen difference $(Ca\text{-}C\bar{v})_{O_2}$ is much greater to meet the metabolic demands. At first glance, body position at $+G_z$ did not make a difference; however, the decrease in SV or $\dot{Q}$ and increase in HR are greater in the erect than in the seated position. This difference is presumably due to the greater degree of venous pooling in the erect than in the seated position. The cardiovascular adjustment to 2 and 3 G_z can apparently overcome the increased stress of gravity as the cardiovascular system appears to be in steady state with the only compromise being a reduced cardiovascular reserve. This reduced reserve could become a limitation when the subject is asked to exercise.

In spite of the apparent adjustment to increased G_z discussed above, it is well known that subjects cannot sustain $+G_z$ for very long. We attempted to expose 6 subjects to 32 min resting experiments at 1 and 3 G_z. The data from these experiments are presented in table III. The $+2$ G_z protocol was tolerated for 20–28 min, while $+3$ G_z was tolerated for only 12–20 min by which time the subjects developed narrowing peripheral vision. The subjects appeared to maintain their initial adaptations to $+G_z$. Resting $\dot{V}_{O_2}$ increased with exposure time, especially at 3 G_z, while $\dot{Q}$ was sustained at a level lower than that at 1 G_z until just prior to the decompensation when $\dot{Q}$ decreased (~20%). HR increased as a function of G_z exposure time up to near maximal exposure time when it decreased. Linnarsson [20] has shown that $\bar{P}a$ is increased at $+G_z$ initially; however, as exposure time increases, there is a decrease of $\bar{P}a$ resulting in an inability of the circulatory system to

Table II. Resting cardiovascular response to increased G_z

		+1 G_z	+2 G_z	+3 G_z
$\dot{V}_{O_2}$, liters · min^{-1}	a	0.29	0.32	0.35
	b	0.25	0.29	0.40
$\dot{Q}$, liters · min^{-1}	a	7.3	5.9	5.6
	b	5.3	4.4	4.3
SV, ml	a	105	66	50
	b	70	47	46
HR, beats · min^{-1}	a	68	89	115
	b	76	98	115
$\bar{P}a$, mm Hg	a	95	107	115
	b	–	–	–
$(Ca\text{–}\bar{C}\bar{v})_{O_2}$, liters O_2 · l_b^{-1}	a	4.1	5.4	8.1
	b	4.8	7.1	8.4

a = Average data from refs 6, 13, 20, 23, and 25; b = average data from our laboratory for the erect posture.

Increased Gravitational Force (+G_z)

When going from the supine to erect posture, gravity pulls 200–500 ml of blood into the dependent limbs, resulting in a decrease in $\dot{Q}$ and $\bar{P}a$ and an increase in HR. Under normal conditions, the drop in $\bar{P}a$ is not sufficient to lead to orthostatic intolerance. If an individual has a pathological condition or altered cardiovascular reflexes as occurs in the adaptation to microgravity, the effect of gravity may lead to orthostatic intolerance. To this end, studying normal subjects in an increased G_z environment may provide insight into the feedback mechanisms involved in the prevention of or tolerance to orthostatic hypotension. Many studies of G_z tolerance have been conducted; however, relatively few have measured cardiovascular variables during steady state adjustment to increased G_z [6, 13, 20, 23, 25]. Data from these studies are combined with data from our studies in table II. Inasmuch as man can only sustain 3 G_z when unassisted by a G-suit or straining, only data at 1, 2 and 3 G_z are presented.

As indicated in table II, there is an increase in $\dot{V}_{O_2}$ with increasing G-load; this increase is most dramatic at 3 G_z. SV is markedly reduced at 2 and 3 G_z when compared to 1 G_z; this results in a decreased $\dot{Q}$ in spite of the dramatic increase in HR. The decreased $\dot{Q}$ is offset by a dramatic increase in TPR as $\bar{P}a$ actually increases at 2 and 3 G_z when compared to 1 G_z and the

support the heart-brain pressure gradient, resulting in inadequate brain perfusion. There is a progressive fall in SV and increase in HR during $+G_z$; however, the decrease in $\bar{P}a$ is much greater than would be expected from the decreased $\dot{Q}$ alone. This suggests that the initial increase in TPR cannot be sustained at either 2 or 3 G_z.

A possible countermeasure to the initial and/or progressive decrease in SV during $+G_z$ exposures could be the muscle-pumping action to increase the VR and therefore SV. In early studies [6, 23], it was suggested that low levels of exercise supported the cardiovascular system during increased G_z; it was already well known that straining maneuvers assist G_z tolerance [2, 10, 17]. No studies, however, follow the cardiovascular variables over a period of constant G_z. We used low levels of exercise ($\dot{V}_{O_2}$ = 0.6–1.0 liters · min^{-1}) during 32 min of 2 and 3 G_z. All 6 subjects completed 32 min at 2 and 3 G_z. with a $\dot{Q}$ that was 10–15% above rest and a HR not significantly different from rest at $+G_z$. Both HR and $\dot{Q}$, and presumably $\bar{P}a$, were maintained for the entire 32 min. It would appear that muscle and abdominal/thoracic pumping assisted VR sufficiently to increase $\dot{Q}$ and maintain the increased value for the exposure period.

Adaptation to Work

Although low levels of exercise during $+G_z$ experiments might be useful, their effectiveness during weightlessness remains to be investigated. In addition, the balance between increased VR due to muscle pumping and the increased demand for muscle blood flow and $\dot{Q}$ at increased and decreased G_z should be examined at higher workloads. Data are presented in table IV for the cardiovascular responses to exercise at 0-G (supine), +1 and 3 G_z.

Under 1 G_z conditions, $\dot{Q}$, HR and $\bar{P}a$ increase linearly with $\dot{V}_{O_2}$ until their maximal values are reached. Under simulated 0 G_z (supine), resting is higher than 1 G_z, HR is lower and $\bar{P}a$ is similar. As $\dot{V}_{O_2}$ rises, $\dot{Q}$, HR and $\bar{P}a$ increase in the 0 G_z condition; however, the differences between 0 and 1 G_z disappear at exercise levels of ~2.0 liters O_2 · min^{-1}. When compared to 1-G_z values, $\dot{Q}$ is lower at rest and at all levels of exercise at 3 G_z, while HR is significantly greater; $\bar{P}a$ is also elevated. The delivery of O_2 to tissues is increased in all G_z conditions by increased SV and HR; however, under $+G_z$ conditions, HR dominates while under 0 G_z, SV plays a greater role. The subjects appear to adapt to exercise under all G_z conditions, but the

Table IV. Cardiovascular responses to exercise at 0 G, +1 G_z and +3 G_z for seated exercise from the literature (a) and for our erect exercise data (b)

Variable	$\dot{V}_{O_2}$, liters · min^{-1}			
	G_z	rest	1.0	2.0
$\dot{Q}$, liters · min^{-1}	0	7.3	12	15
	1	6.3	11	16
	3a	5.6	10	–
	3b	4.8	8	13
HR, beats · min^{-1}	0	68	90	137
	1	72	99	134
	3a	115	150	–
	3b	115	148	172
$\bar{P}a$, mm Hg	0	94	106	122
	1	95	105	125
	3a	115	125	–
	3b	–	–	–

mechanisms of the adjustments are different. For example, at a $\dot{V}_{O_2}$ of 1.0 liters · min^{-1}, the $(Ca\text{-}C\bar{v})_{O_2}$ is 8, 9.1, and 12 liters O_2/1 blood for 0, 1, and 3 G_z, respectively. At the higher workload $(Ca\text{-}C\bar{v})_{O_2}$ was 13, 13, and 15 for 0, 1 and 3 G_z, respectively. As higher workloads are achieved, the increased VR due to the supine posture is no longer evident, while on the other hand, the decreased VR due to $+G_z$ becomes a major limitation to $\dot{Q}$. The limit to the adjustment of the cardiovascular system can be considered to be the maximal aerobic power. Previous work has shown that the $\dot{V}_{O_2}$ max in the supine position is 10–15% lower than in the erect position in spite of the greater SV at lower workloads [5, 24, 28].

On the other hand, it is obvious from table IV that the maximal $\dot{V}_{O_2}$ at 3 G_z is significantly lower than at 1 G_z (~40%). In spite of the limitations of increased G_z on the cardiovascular system, exercise can be carried out at least at modest workloads while the response of the cardiovascular system at 0 G_z is not appreciably different than at 1 G_z. It should be noted, however, that at low exercise levels ($\dot{V}_{O_2} < 1.0$ liters · min^{-1}) 3 G_z can be tolerated for 30–45 min while at higher workloads ($\dot{V}_{O_2} > 1.0$ liters · min^{-1}), G_z tolerance time is reduced to 16–24 min. This would suggest that the cardiovascular system is not in a true steady state. Further investigation into this area is needed.

Adapation to the space environment requires first the adjustment to weightlessness and then re-adaptation to gravity. Astronauts will be required to perform work in both a weightless environment and under increased gravitational force. The ability to adapt to exercise over time is critical to successful adaptation. Exercise during weightlessness is apparently not limited at submaximal levels. As discussed above, under increased G_z conditions, there is an initial adjustment of the cardiovascular system; however, in a relatively short period of time, the cardiovascular system cannot meet the demands of G_z plus exercise. It is not apparent that these observations could be applied to a 1 G_z environment following adaptation to weightlessness; however, the response to 1 G_z after adaptation to weightlessness seen as cardiovascular deconditioning would appear similar to that made in going from 0 to 1 G_z. In studies by Convertino [8, 9], exercise performance after 10 days of HDT or bed rest (0 G_z) demonstrated that $\dot{V}_{O_2}$ max was lower (~8%), submaximal HR was greater (~5%), and the anaerobic threshold lower. This author concluded that PV lost during adaptation to weightlessness resulted in the observed cardiovascular deconditioning. Interestingly, Convertino's findings are qualitatively similar to the data where 2 G_z is compared to 1 G_z.

In summary, it appears that man is capable of adapting to a weightless environment. Although the application of the Gauer-Henry hypothesis to this adjustment needs to be reconsidered, there appears to be a decrease in PV as well as in sympathetic tone after 2–3 days of 0 G_z. The role of the hydration state of the subjects needs further investigation, as there appears to be complete adjustment to 0 G_z within 8 h without a decrease in PV (when subjects are allowed to dehydrate mildly). In actual space flight, space motion sickness is experienced at least mildly by most astronauts. This may alter the hydration state for the first few days, and once relieved by rehydration, may lead to the decrease in PV that is typically reported. Hydration changes account for the inability to re-adapt to gravity upon return to earth and may lead to the inability to function when landing on other planets. Apparently exercise, per se, does not serve as an effective countermeasure. Even though $+G_z$ tolerance was improved, it did not persist long enough to maintain the steady state.

Given sufficient adjustment time, man can re-adapt to gravity; however, the dynamics of the adjustments of the cardiovascular system need further investigation. It is clear that, if man is to successfully adapt to the space environment and return from it, we must prevent cardiovascular deconditioning that develops during the weightless period by either uncov-

ering and interfering with the mechanism that causes it or by developing effective countermeasures. These could presumably be used not only during weightlessness but also during re-entry. By identifying and using such countermeasures, we may be able to effectively extend man's interplanetary initiatives as he learns to cope with gravitational force in much the same way as he deals with other environmental variables.

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RESEARCH ON THE ADAPTATION OF SKELETAL MUSCLE TO HYPOGRAVITY: PAST AND FUTURE DIRECTIONS

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ABSTRACT

Our current understanding of hypogravity-induced atrophy of skeletal muscles is based primarily on studies comparing pre- and post-flight properties of muscles. Interpretations are necessarily qualified by the assumption that the stress of reentry and readjustment to terrestrial gravity do not alter the parameters being analyzed. The neuromuscular system is highly responsive to changes in functional demands and capable of rapid adaptation, making this assumption questionable. A reexamination of the changes in the connective tissue and synaptic terminals of soleus muscles from rats orbited in biosatellites and sampled postflight indicates that these structural alterations represent adaptative responses of the atrophic muscles to the increased workload of returning to 1 G, rather than hypogravity per se. The atrophy of weightlessness is postulated to result because muscles are both underloaded and used less often. Proper testing of this hypothesis requires quantitation of muscle function by monitoring electromyography, force output and length changes during the flight. Experiments conducted in space laboratories, like those being developed for the Space Shuttle, will avoid the complications of reentry before tissue sampling and allow time course studies of the rate of development of adaptive changes to zero gravity. Another area of great importance for future studies of muscle atrophy is inflight measurement of plasma levels of hormones and tissue receptor levels. Glucocorticoids, thyroid hormone and insulin exert dramatic regulatory influences on muscle structure. Prevention of neuromuscular atrophy becomes increasingly more important as spaceflights increase in duration. Definition of the atrophic mechanism is essential to developing means of preventing neuromuscular atrophy.

INTRODUCTION

Skeletal muscle atrophy, especially of the antigravity muscles, continues to represent a major problem to long term habitation in the hypogravity environment of space by man. Research in this area has been directed toward defining the atrophic process and finding means of preventing it. The primary issues, as yet unanswered, are to define what attributes of weightlessness are deleterious and to determine whether the atrophic process is similar to that occurring on Earth during periods of inactivity such as extended bed rest. Does the hypogravity-induced atrophy simply represent quantitative and qualitative changes in the components of the cells of the neuromuscular system? From information available to date it is not possible to rule out that a more serious situation exists in that there is cell death as in denervation atrophy. If the latter is true, then unique means of preventing and reversing muscle wasting will have to be developed.

Our current understanding of hypogravity-induced atrophy is based largely on the results of animal experiments flown in the Cosmos series of biosatellites and human studies during the Gemini, Skylab, Apollo and Soyus missions [1]. As recognized by previous investigators, characterization of the effects of hypogravity on the neuromuscular and other systems has been handicapped by the return of the biosatellites to 1 G and the lapse of 4.5 hrs to 2 days prior to tissue sampling. Interpretations must be qualified by the assumption that the parameters being analyzed are not altered during this period. Unfortunately, dramatic changes can, and probably do, occur in the neuromuscular system, rendering this assumption highly questionable. In the present discussion, selected issues will be reassessed from past biosatellite data to form a framework upon which the need for specific future directions of research will be discussed.

POSTFLIGHT TISSUE SAMPLING OF RATS FLOWN IN BIOSATELLITES

Muscle Fiber Atrophy and Connective Tissue Proliferation: The soleus muscles of rats flown

22 days aboard Cosmos 605 were examined morphologically on the second day postflight [2]. Muscle wet weight had decreased significantly by 32%. Marked focal edema of the endo- and perimysial layers and increases in connective tissue cells were found as well as focal disruption of muscle fibers. It was theorized that these changes were due to the hypokinesia of weightlessness which produced blood stasis, edema and connective tissue proliferation that interfered with the vascular trophism of muscle fibers and caused their partial disintegration. Similar changes were reported for an Earth-based model of hypokinesia which involved rigidly-restraining rats from moving. Following a few days of restraint, the edematous appearance and focal increase in connective tissue cells was evident in the soleus muscles [3]. Unlike the muscles from rats flown on Cosmos 605, muscle fiber atrophy was not present. In this case, the hemodynamic disorder was postulated to have developed from a combination of mechanical compression of the hindlimb vessels by the restraint mechanism, and from inadequate venous return from the quiescent muscle which was not exerting its normal pumping action to aid venous return. Analysis of soleus muscles 4.5 to 5 hrs postflight, as occurred for Cosmos 782 and 936, revealed that the edema was absent and therefore, it must be a postflight phenomenon occurring in the first 2 days [4]. It was concluded that the deconditioning of the muscular and vascular systems during weightlessness rendered the muscle incapable of handling the increased blood flow which accompanied resumed movements and therefore, stasis, followed by edema, resulted. No direct measurements of blood flow were made in this system. More recently, blood flow was demonstrated to be reduced during drug-induced flaccid paralysis and may have played a role in atrophy [5]. However, we would like to propose an alternative explanation for the biosatellite data:

Jablecki et al. induced rapid hypertrophy of normal soleus muscles in rats by tenotomizing synergistic muscles, i.e., the distal tendons of the plantaris and gastrocnemius muscles were severed and the soleus tendon spared, resulting in the soleus muscle acquiring the additional workloads of the tenotomized muscles [6]. After 2 days of contracting against the increased workload, the solei exhibited widened intercellular areas with a proliferation of fibroblasts and macrophages. The fibroblasts were heavily labeled following injection of a radiolabeled RNA precursor, uridine, and there was a definite increase in connective tissue matrix seen ultrastructurally. Proliferation of the connective tissue was found biochemically for hypertrophying muscles in a similar experiment [7]. The transition of the atrophic muscles from the hypogravity environment to terrestrial gravity constituted a dramatically increased workload and stimulated rapid growth. In the restricted movement model, the rat would be expected initially to struggle strenously to free himself. The soleus muscles would be contracting isometrically while being held in a lengthened state which together would promote hypertrophy [8]. The so-called "edema" appeared to be the growth response of the connective tissue to the increased force rather than venous congestion. Although vascular congestion cannot yet be ruled out for the rapid hypertrophy experiment, the vascular and muscular systems of the soleus muscles at the onset of the increased workload were normal, unlike those of the deconditioned muscles of flight animals, and presumably were capable of handling the increased blood flow.

Degeneration of Neuromuscular Junctions: The motor innervation of skeletal muscles of adult rats consists of myelinated preterminal axons which synapse at the endplate as a fine terminal arborization (Figure 1). At the ultrastructural level, spherical synaptic terminals filled with "50 nM" vesicles and mitochondria lie within synaptic clefts formed by the plasmolemma of the muscle fiber (Figure 2).

Soleus muscles from Biosputnik 936 were processed for ultrastructural analyses 4.5 to 9 hrs postflight [9]. Synaptic terminals in the muscles from vivarium control animals exhibited high synaptic vesicle density and intact mitochondria similar to that in Figure 2. Terminals in the muscles from rats flown in space had significantly fewer synaptic vesicles and the mitochondria were markedly swollen. These changes were thought to represent the initial stages of degeneration of terminals resulting from hypokinesia. On the contrary, a more plausible explanation is that the changes were the result of hyperactivity of the neuromuscular junctions following the return to 1 G. We conclude this because electrical stimulation of the nerves of normal muscles produces comparable decreases in synaptic vesicle number and mitochondrial properties within a few hours [10,11]. It is evident from this and preceding examples that inflight tissue sampling, uncomplicated by the stresses of reentry and early adaptive responses to 1 G, is essential for characterizing muscle atrophy. This will be possible in the Space Laboratory carried into orbit by the Space Transportation System.

RESPONSES OF MOTOR INNERVATION TO ALTERED ACTIVITY

Necessity of Inflight Studies of Motor Innervation: There are sufficient indications from Earth based and biosatellite studies that the innervation of skeletal muscle is disrupted during both disuse and hyperactivity to warrant concern about the integrity of this system. Tenotomy reportedly resulted in decreases of average motor endplate area, the size of the terminal arbor, the diameter of the myelinated axons and disturbingly, the total number of

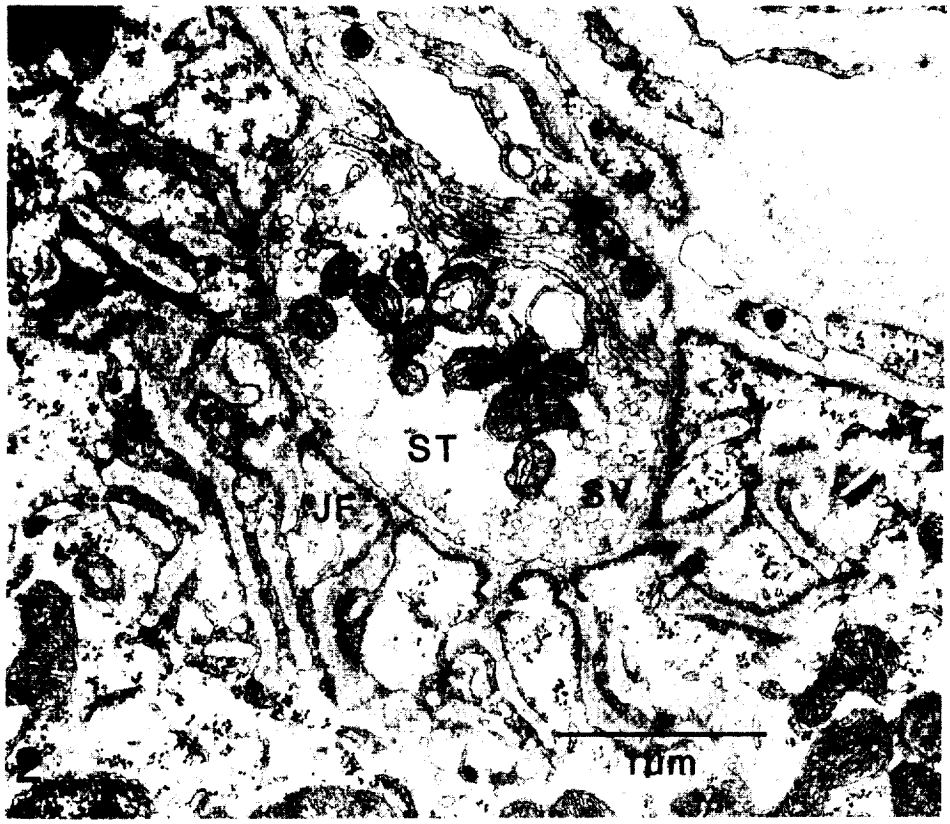

Figure 1. Two neuromuscular junctions of a normal rat skeletal muscle demonstrated by a combination of silver impregnation of the motor axons and histochemical staining of the endplate acetylcholinesterase. The cross-striations of the underlying muscle fibers are visible. The axons consist of preterminal (PT) myelinated portions and nonmyelinated terminal branches (arrows) ramifying over the cholinesterase reaction product (E). At the ultrastructural level, a cross section of a terminal branch would appear similar to Figure 2. Bar equals 50 µm.

Figure 2. A portion of a rat neuromuscular junction in a normal soleus muscle. The synaptic terminal (ST) lies within a depression, the synaptic cleft, and apposes the postsynaptic membrane of the muscle fiber which is thrown into numerous junctional folds (JF). Within the terminal, "50 nm" clear synaptic vesicles (SV) are clustered near the sides of the terminal adjacent to the postsynaptic membrane. Mitochondria (M) are aggregated centrally. Bar equals 1 µm.

axons in the muscle nerve [12,13]. Immobilization resulted in a significant decrease in average axon diameter, but the total number of myelinated axons was unchanged [14]. Interestingly, the axons increased in diameter in the nerves of the muscles contralateral to the intact side. Chronic exercise training increased axon diameters in the mouse [15]. Rapid hypertrophy of the rat soleus muscle following inactivation of synergistic muscles and strenuous exercise produced enlargement of the motor endplates and preterminal motor

axons [16]. Following short bouts of intense exercise, swelling of motoneurons and increased acid phosphatase activity were found [17,18]. Acid phosphatase activity increases when axons were injured [19]. In the restricted mobility experiments, destruction of end-plates, sprouting of motor axons and loss of muscle fibers were detected in the rat soleus muscle [20]. Thickening and coarsening of nerve terminals was reported for rats orbited in the Cosmos biosatellites [21]. It cannot be determined without further experimentation whether these changes in the flight muscles resulted during reentry to Earth's gravity or the exposure to hypogravity. Inflight sequential biopsies of the neuromuscular system are required to resolve this issue.

Masking of Motor Innervation Deficits by Compensatory Mechanisms: Large losses of motor axons could occur without an obvious long term deficit because partial denervation of a muscle induces the remaining healthy axons to sprout and reinnervate the orphaned muscle fibers [22]. Function is returned relatively quickly because of the short distance for axon growth. Muscle tension would fall initially following axon loss, but it would return to normal as reinnervation and compensatory hypertrophy of the innervated muscle fibers proceeds. The compensatory process could conceivably mask a motor nerve deficit after an initial jaunt into space. Even though the system repairs itself, this does not mean that there is no reason for concern because the capacity of axons to sprout is limited [22]. Repeated exposures to weightlessness could eventually exhaust this mechanism and the neuromuscular deficit would become more pronounced and eventually, debilitating. The integrity of the motor innervation should be assessed by light and electron microscopic analyses of inflight tissue biopsies.

NEEDS FOR QUANTITATION OF MUSCLE FUNCTION

Definition of Muscle Function: Muscle atrophy of hypogravity is postulated to occur because the muscles are both underloaded and used less often. To test this hypothesis in animal experiments requires simultaneous measuring the pattern of muscle activity (electromyography), force output and muscle length. These data are obtained by direct wiring or biotelemetry of electromyography (EMG) signals from implanted intramuscular electrodes, force transducers attached to the muscle tendon and a length gauge anchored in parallel with the muscle of interest [23,24]. The EMG signals provide information about the duration of contraction and average frequency of firing. Additional information is extractable from the EMG signal by frequency spectral analysis which treats the muscle action potentials as a summation of simpler waveforms and differentiates the complex EMG signals into basic components occurring in preselected frequency bands [25]. The power (amplitude) of each of these frequency components is compared. The dominant or mode frequency of a spectral histogram shifts significantly in myopathies and neuropathies [26]. These changes correlate with variations in the shape and duration of the normal bi- and triphasic muscle action potentials to more polyphasic potentials. This approach proved a sensitive measure of muscle dysfunction in astronauts having experienced as little as 9 days of hypogravity in the Apollo-Soyuz space mission [27,28]. Postflight fatiguability increased significantly, and this was indicated by spectral power shifts into lower frequencies during exercise testing. Muscle atrophy was indicated by an increase of the mode frequency from the preflight baseline 55 Hz band to the 95 Hz band. Spectral analysis performed pre-, in- and postflight on astronauts would allow definition of the onset and degree of atrophic changes and provide valuable feedback on the effectiveness of inflight prophylactic measures and postflight recovery procedures.

Length is an important parameter because the strength of a muscle contraction is dependent on the degree of overlap of the actin and myosin [29]. A highly active muscle, assessed electromyographically, can generate a small amount of tension if it is either extended or shortened greatly beyond its normal working midrange. Measurements of length and EMG activity in unrestrained cats proved very effective in defining the differential participation of soleus and medial gastrocnemius muscles in standing, walking, running and jumping activities [24,30]. The soleus muscle was very active in standing whereas the medial gastrocnemius was nearly silent. As the intensity of the movement increased from walking to running the medial gastrocnemius became more active and generated maximum force only during jumping. Pre-, in- and postflight monitoring of these parameters in instrumented animals would provide valuable data on altered muscle function in weightlessness, the efficacy of prophylactic measures, the recovery process, and for comparison with biochemical and anatomical changes in the muscles.

Advantage of Quantitating Muscle Function: A survey of studies examining muscle adaptation to hypogravity and terrestrial model systems reveals a serious lack of quantitation of muscle function. Without this information, there is no precise definition of the conditions to which the muscle is adapting. For example, consider the following situation in which the application of electromyography to assess muscle activity greatly advanced the understanding of muscle atrophy produced by tenotomy. Cutting one tendon of a muscle and allowing the muscle to hypershorten results in severe atrophy. Previous investigators hypothesized that the atrophy was the consequence of the combination of removing the

weight bearing function of the tenotomized muscle and decreasing its stretch-activated contractile activity. While atrophy occurred in tenotomized soleus muscles of the cat, rat and rabbit, daily EMG recording revealed, unexpectedly, that the normal pattern of nearly continuous activity was dramatically decreased in all solei, except that of the cat in which contractile activity remained at the control level [31,32,33]. In fact, totally eliminating activity of tenotomized muscles by spinal cord transection, which removed supraspinal activation of soleus motoneurons, markedly retarded muscle atrophy. Conversely, hyperactivity, achieved by electrical stimulation of the nerve supplying the tenotomized muscle, significantly accelerated muscle degeneration [34]. The changes in muscle use following tenotomy were not uniform in different species which indicated that neither workload nor activity per se were the primary causes of atrophy. The common factor was recognized to be hypershortening of active muscle fibers which resulted in decreased fiber diameter and disruption of their myofibrils. This conclusion would not have been reached without the knowledge of activity patterns.

Motor Unit Function: Large electrodes are used to monitor gross muscle activity and smaller electrodes are used to assess function of single motor units i.e., all of the muscle fibers innervated by a single α motoneuron [35,36]. Electrode configuration and placement are important because all human skeletal muscles are composed of a mixture of fast and slow motor units which differ in their normal patterns of activity. Fast units are active in brief bursts occurring infrequently whereas slow units exhibit frequent bouts of nearly continuous activity. Chronic recording of EMG in a variety of human muscles demonstrated that muscles with the highest proportions of slow fibers were active more often than those containing a high percentage of fast units [37]. Patterns of EMG activity were shown for the rat diaphragm and to correlate with the fiber type population in the field of the recording electrodes [38]. The rat soleus muscle, an antigravity muscle, exhibits continuous low frequency (10 Hz) activity when the rat is standing in 1 G. Immobilization of the hindlimb shifted muscle activity to a phasic pattern, i.e., a pattern of infrequent, brief trains of 10 Hz contraction [36]. One would predict a similar shift in hypogravity. Investigation of this hypothesis requires quantitation of muscle function from humans and animals in space.

NEED FOR INFLIGHT MONITORING OF HORMONES

Glucocorticoids: Inactivity of weight bearing muscles due to immobilization appears to increase the number of glucocorticoid receptors in the muscle, and presumably results in an increased sensitivity to circulating glucocorticoids [39,40,41]. Reduction of muscle mass and an impairment of performance may then be expected to ensue in the immobilized or disused muscles. It remains to be determined whether muscles subjected to disuse from weightlessness also increase their receptor number in parallel with the selectivity and degree of atrophy that are especially noteable in postural muscles e.g., the soleus muscle.

The consequence of increased numbers of glucocorticoid receptors in disused muscles may be augmented by increases in the concentrations of plasma glucocorticoids. Although inflight measurements of plasma corticosteroids are not available, the adrenal hypertrophy observed in rats flown in biosatellites suggests that a chronic stress response occurs on exposure to weightlessness for 20 days [39,40] in which case plasma corticosteroids should be elevated. Moreover, significant increases in corticosteroid dependent enzymes (glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase) in the livers of rats also indicate that plasma corticosteroid levels were elevated during spaceflight [39].

Ground-based research and inflight muscle sampling in test animals is strongly indicated with respect to analyses of glucocorticoid receptors as well as the concentrations of glucocorticoid and other hormones in plasma such as reported for man in spaceflight by Leach et al. [39].

Insulin: An interesting effect of immobilization on skeletal muscle, and one which we might expect to find produced also by weightlessness, was observed with regard to insulin sensitivity. The in vitro uptake of 2-deoxyglucose and glycogen synthesis by soleus muscles excised from the immobilized hindlimb of mice was significantly decreased in response to insulin as early as 24 hrs after the beginning of immobilization [42]. The direct demonstration of reduced insulin sensitivity of inactive skeletal muscles of mice is in keeping with the commonly observed reduction in insulin sensitivity of man during conditions of inactivity induced by extended bedrest [43]. Whether there are relationships between postural activity, muscle fiber types, susceptibility to atrophy, and insulin sensitivity of specific muscles in the limbs of experimental animals are subject for future investigation.

Thyroid Hormone: The potential importance of plasma hormone concentrations in regulating muscle characteristics and, consequently, performance is illustrated in the case of thyroid hormone. We have recently found that lowering thyroid hormone levels by thyroidectomy dramatically shifts the myofibrillar ATPase activity of the fast fibers in the rat soleus muscle from high to low activity with no apparent gross change in the use of the hindlimb

[44]. That the decreased level of thyroid hormone was working through an intact innervation was indicated by the lack of a similar response in denervated muscles of hypothyroid rats. Thus, in future studies of flight animals and man blood analyses of relevant hormones should be monitored inflight to ascertain their possible contribution to muscle atrophy.

FUTURE DIRECTIONS OF NEUROMUSCULAR RESEARCH IN SPACE

For the evaluation of the effects of weightlessness on skeletal musculature, one of the primary requirements is tissue sampling during the course of flight. This capability is desirable for two reasons: One is to avoid the complicating effects of reentry acceleration forces as well as the subsequent exposure to the Earth's gravity before muscle sampling or sacrifice of the experimental animal. The second consideration is that an inflight sampling capability would allow time course studies of the rate of development of adaptational changes to zero gravity.

In the case of human subjects, there is good evidence that hypogravity induces the loss of muscle mass and strength in the lower limbs [45]. However, it is not yet known which lower limb muscles are effected most severely and to what degree, particularly with regard to rate of atrophy inflight as well as recovery postflight. Computer assisted tomography of the lower limbs, performed pre- and postflight, may provide quantitative evidence of the reduction in size of specific muscles as well as data concerning their water, fat, and protein content [46,47]. Information regarding the status of individual muscles would be useful in the design of prophylactic exercises.

The metabolic status of skeletal muscle with regard to high energy phosphate compounds is likely to be altered during hypogravity-induced atrophy. Creatine phosphate, ATP, and sugar phosphates may be determined by phosphorus nuclear magnetic resonance (NMR) measurements on excised muscles obtained during the course of the mission from experimental animals and subsequently analyzed in ground based NMR facilities [48,49].

Advancing our understanding of muscle adaptation requires that a substantial emphasis be placed on quantitation of muscle function by measuring the pattern of muscle contraction and tension generation in response to varying workloads. The major theories of hypogravity-induced atrophy, hypodynamia and hypokinesia, can be evaluated with this information obtained from pre-, in- and postflight muscles. In a reverse sense, the validity of using model systems, such as restricted mobility [3] and suspended restraint [50,51], for simulating weightlessness is testable by comparing muscle function in these systems with that obtained in flight. Having suitable models for study could reduce the number of costly flight experiments. Furthermore, the development of prophylactic measures of preventing atrophy is aided by objective measures of the success of the procedures, i.e., determination of the minimum amounts of exercise and artificial gravity required to advert muscle wasting during space flight [45,52].

As man enters the unknown environment of space for longer periods, the continuation of research on his adaptation becomes more crucial. The biosatellite studies of the Russian scientists made important pioneering contributions to this field for which they should be congratulated. The continued cooperation and exchange of information between space scientists of the world should continue because these efforts benefit all peoples.

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